Sellar Remodeling after Surgery for Nonfunctioning Pituitary Adenoma: Intercarotid Distance as a Predictor of Recurrence

Citation for published version:
Raghu, ALB, Flower, HD, Statham, PFX, Brennan, PM & Hughes, MA 2019, 'Sellar Remodeling after Surgery for Nonfunctioning Pituitary Adenoma: Intercarotid Distance as a Predictor of Recurrence', *Journal of Neurological Surgery Part B: Skull Base*. https://doi.org/10.1055/s-0039-1693700

Digital Object Identifier (DOI):
10.1055/s-0039-1693700

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Peer reviewed version

Published In:
Journal of Neurological Surgery Part B: Skull Base

JOURNAL OF NEUROLOGICAL SURGERY — PART B
Skull Base

Sellar remodeling after surgery for non-functioning pituitary adenoma: intercarotid distance as a predictor of recurrence.

Journal:	*JNLS-B*
Manuscript ID	19-Mar-0070.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Raghu, Ashley; University of Oxford, Nuffield Department of Surgical Sciences; University of Edinburgh, Edinburgh Medical School Flower, Hannah ; University of Edinburgh, Edinburgh Medical School Statham, Patrick; NHS Lothian, Department of Clinical Neurosciences Brennan, Paul; University of Edinburgh, Edinburgh Medical School; NHS Lothian, Department of Clinical Neurosciences Hughes, Mark; University of Edinburgh, Edinburgh Medical School; NHS Lothian, Department of Clinical Neurosciences
Keywords:	pituitary adenoma, sella turcica, magnetic resonance imaging, recurrence, intercarotid distance

Sellar remodeling after surgery for non-functioning pituitary adenoma: intercarotid distance as a predictor of recurrence.

Mr Ashley L B Raghu *

BSc (Hons)

MBChB Student, DPhil Student

Edinburgh Medical School, University of Edinburgh

Nuffield Department of Surgical Sciences, University of Oxford

ashley.raghu@linacre.ox.ac.uk

Linacre College, St. Cross Road, Oxford. OX1 3JA

+447760396317

Ms Hannah D Flower

BMedSci (Hons)

MBChB Student

Edinburgh Medical School, University of Edinburgh

hannah_flower@live.co.uk

Mr Patrick F X Statham

MBBS FRCS(SN)

Consultant Neurosurgeon

Department of Clinical Neurosciences, NHS Lothian

patrick.statham@nhslothian.scot.nhs.uk

Mr Paul M Brennan

BSc (Hons), MB BChir, PhD, FRCS(SN)

Senior Clinical Lecturer, Honorary Consultant Neurosurgeon

Edinburgh Medical School, University of Edinburgh

Department of Clinical Neurosciences, NHS Lothian

paul.brennan@ed.ac.uk

Mr Mark A Hughes

BSc (Hons), MSc, MBChB, MAcadMed, PhD, FRCS(SN)

Clinical Lecturer, Neurosurgery Registrar

Edinburgh Medical School, University of Edinburgh

Department of Clinical Neurosciences, NHS Lothian

mhughes4@exseed.ed.ac.uk

*corresponding author

Acknowledgements

Professor Mark Strachan

BSc(Hons) MBChB(Hons) MD FRCP

Honorary Professor, Consultant Physician in Endocrinology and Diabetes

Edinburgh Medical School, University of Edinburgh

Metabolic Unit, NHS Lothian

ABSTRACT

Introduction:

As they grow, pituitary adenoma can remodel the sella turcica and alter anatomical relationships with adjacent structures. The intercarotid distance (ICD) at the level of the sella is a measure of sella width. The purpose of this study was to: (1) assess how ICD changes after transsphenoidal surgery and (2) explore whether the extent of ICD change is associated with tumor recurrence.

Methods:

A retrospective analysis of pre-operative and post-operative coronal MRI scans was carried out by two independent assessors on patients who underwent transsphenoidal surgery for non-functioning pituitary macroadenomas. Pre-operative tumor volume and any change in ICD following surgery were recorded and compared between groups. Logistic regression models of recurrence were generated.

Results:

In 36 of 42 patients, ICD fell after surgery (mean=1.8 mm) and 6 cases were static. At time of follow-up (mean=77 months), 25 had not required further intervention and 17 had undergone second surgery or radiosurgery. In patients in whom no further intervention has yet been necessary, the post-operative reduction in ICD was significantly smaller than in those who required repeat intervention (1.1mm vs.

2.7mm respectively, P<0.01). ICD decrease was weakly correlated with tumor volume (r=0.35). ICD decrease was a significant predictor of recurrence (odds ratio 3.15; 95% confidence interval, 1.44-6.87), largely independent of tumor volume.

Conclusion:

For most patients, ICD falls following surgical excision of a non-functioning pituitary macroadenoma. A greater reduction in ICD post-surgery appears to predict recurrence. Change in ICD shows promise as a radiographic tool for prognosticating clinical course after surgery.

Keywords: Pituitary adenoma, sella turcica, magnetic resonance imaging, recurrence, intercarotid distance

ARTICLE

Introduction

Pituitary tumors frequently expand the sella turcica, a finding utilized in the pre-computed tomography era to help diagnose their presence on plain radiographs. The lateral confines of the sella are the right and left cavernous sinuses, and the structures they house. This area can be remodeled and/or invaded by tumor. The medially positioned cavernous internal carotid artery segment can become encased or distorted. Sella width can be defined by the distance between carotid sulci in the lateral walls.[1] As such, the distance between the medial borders of these cavernous arterial segments (intercarotid distance - ICD) is a close surrogate of sella width and is amenable to magnetic resonance imaging (MRI) measurement.

ICD has received interest mostly as a means of defining the narrow surgical corridor in transsphenoidal surgery. ICD increases from infanthood to adulthood and shows a relatively large inter-individual variation (12.8-23.9 mm).[2–4] Likewise, with pituitary adenoma *in situ* ICD variation is large[4,5] and can inform surgical candidacy and planning. The ratio of tumor diameter to pre-operative ICD has also recently been used to predict extent of resection[6]. Giant pituitary adenomas show obvious widening of the sella.[4] Although tumor height and width appear to correlate with pre-operative ICD,[7] to what extent sella widening occurs with smaller pituitary adenomas is less well defined,[4,7–10] as are the factors determining this process. Furthermore, it is difficult to confirm expansion is secondary to tumor as there is rarely a baseline historic scan that predates the tumor's presence.[3,4]

Tumors displace or compress adjacent structures by exerting pressure on them. This pressure should be relieved by surgical decompression. Previous work has shown that following transsphenoidal resection of pituitary adenoma, there is an intra- and post-operative reduction in the ICD in 26-52% of cases.[11,12] Larger contraction was not associated with greater pre-operative tumor size. Another group noted that Knosp grade[13] 3 and 4 tumors (i.e. tumors extending at least beyond the lateral margin of the cavernous ICA) were associated with large post-operative ICD contraction (>2mm).~~,~~[11] H~~h~~owever this has not been replicated elsewhere,~~.~~[12] and may have been related to inclusion of microadenoma with necessarily low Knosp grade and mechanical implausibility to widen the sella.

After surgery, simple tools for evidence-based prognostication of recurrence are limited. Gross-total resection conveys a lower risk of recurrence than leaving residual tumor, and smaller tumor size at operation decreases the likelihood of leaving residual tumor.[14,15] Giant tumors in particular show a high likelihood of clinically relevant recurrence.[16] This study aimed to measure changes in ICD following surgery for a series of non-functioning macroadenomas, and to relate this change to pre-operative tumor volume. We reasoned that proven ability of an adenoma to laterally expand the sella may be related to a more hostile growth profile. As such, after tumor resection, a greater fall in ICD may be an unfavorable prognostic sign and signify a higher chance of post-operative recurrence.

Patients and Methods

191 consecutive patients who had first transsphenoidal surgery between 2007 and 2013 for non-functioning pituitary macroadenomas were retrospectively reviewed from medical records. 149 patients had no available pre-operative MRI brain scan, leaving 42 patients remaining to study. Tumor immunohistochemical subtype was retrieved from pathology reports. Estimated pre-operative tumor volume was calculated as an ellipsoid using maximal tumor dimensions from the latest pre-operative scan.[17] Time to any secondary interventions (second surgery or radiosurgery) and duration of follow up were measured. Pre-operative Knosp score

was assessed and post-operative residuum categorized: gross total resection (GTR) – no visible tumor remnant; sub-total resection (STR) - small rim/capsule; 'microadenoma' - cumulative residuum < 10 mm in maximal dimension; 'macroadenoma' -cumulative residuum ≥ 10 mm in maximal dimension.

Two assessors, blinded to post-operative care, independently measured ICD. ICD was measured on the picture archiving and communication system (PACS) image-viewing platform (Carestream Health UK, Limited), where measurements are given to the nearest 10 μm. The latest pre-operative MRI scan and the earliest post-operative MRI scan were selected. Pre-operative and post-operative coronal images were compared with strict care to select comparable sections. Images were chosen which best showed the four transversely coursing segments of the cavernous and ophthalmic internal carotid arteries. Sections showing the clinoid, anterior vertical cavernous, posterior vertical cavernous and lacerum segments were avoided. When more than one section satisfied these requirements, the most dorsal image was chosen. ICD was measured as the distance between the medial wall of two cavernous internal carotid arteries. The difference in ICD (Δ-ICD) between pre- and post-operative scans was calculated ($ICD_{pre\text{-}operative} - ICD_{post\text{-}operative}$), and reported as a mean of the two observers. Therefore, *positive* Δ-ICD values represent *contraction*, and *negative* Δ-ICD values represent *expansion*. Static Δ-ICD was defined as a difference of 0.5 mm or less.

The intra-class coefficient was calculated as a measure of inter-observer reliability. 10 patients were randomly selected, and their Δ-ICD calculated a second time. Mean discrepancy with the first value gave the mean intra-observer variability.

Progression to secondary intervention was used as an objective surrogate of recurrence. In order to evaluate the utility of Δ-ICD and tumor volume (continuous predictors) in predicting recurrence (categorical outcome) we constructed binary logistic regression models.

Results

The patients, 23 male and 19 female, had a mean age of 56 years at surgery (range: 23-90 years). 6 tumors had a major cystic component and ~~I~~immunohistochemical subtypes were mostly clinically silent gonadotroph (50%) and null cell (45%). Knosp scores were 45% non-invasive-type (0-2) and 55% invasive-type (3-4) (see Table 1).

Post-operative scans were a median of 4 months after surgery. ICD decreased after surgery by a mean of 1.8 mm (range -0.2 to 6.4 mm) and 6 cases were static. 98%, 85%, 69%, 29% demonstrated a Δ-ICD > 0 mm, > 0.5 mm, > 1.0 mm, > 2 mm respectively.

Table 1. Pre-operative Knosp grade and post-operative residuum

Knosp grade	Total	GTR	STR	< 10mm	≥ 10mm
0	2	1	0	1	0
1	7	1	1	1	4
2	10	1	1	1	7
3	11	0	1	5	5
4	12	0	0	0	12

Figure 1. Quartile distribution of intercarotid distance (ICD) decrease after surgery

The mean intra-observer variability was 0.4 mm and mean inter-observer variability was 0.6 mm. The intraclass correlation coefficient was 0.857, demonstrating good inter-observer reliability.

25 patients had no further intervention and 17 had a second surgery or radiosurgery. The mean post-operative follow-up was 77 months, with secondary interventions occurring at a median of 21 months. In patients in whom no further intervention has yet been necessary, the Δ-ICD was smaller (less contraction) than in those who have gone on to require repeat intervention (1.1 mm vs. 2.7 mm respectively, $P<0.01$). Estimated pre-operative tumor volume was smaller in those who went on to require repeat intervention (48 mm^3 vs. 99 mm^3 respectively, $P<0.01$). Δ-ICD was weakly correlated with tumor volume ($R = 0.35$). 6 cases (14%) demonstrated a very large decrease in ICD (> 2 mm) despite a small tumor volume (< 50 mm^3) (see Fig. 2).

Figure 2. Plot comparing pre-operative tumor volume and Δ-ICD for each patient. Patients 6, 22, 28, 32, 39, 41 have small tumors but large decrease in ICD. Tx = treatment

Univariate binary logistic regression found Δ-ICD a superior predictor of secondary intervention than tumor volume at time of diagnosis (see Table 2~~1~~). In bivariate modelling, Δ-ICD remained a significant predictor of secondary intervention, whereas tumor volume marginally failed significance. In trivariate modelling with an (Δ-ICD x volume) interaction term, χ^2 was not significant for inclusion in the regression model (0.015, P = 0.903). The univariate model found a 130% increase in the odds of recurrence for a 50 mm^3 increase in tumor volume, and a 215% increase in odds of recurrence for a 1 mm increase in Δ-ICD (i.e. 1 mm contraction of sella width). The bivariate model found that for holding tumor volume fixed, there was a 194% increase in odds of recurrence for a 1 mm increase in Δ-ICD.

Table ~~1~~2. Results of binary logistic regression models for the outcomes of progression to secondary intervention or not, with Δ-ICD and tumor volume as predictors.

Predictor	χ^2	Nagelkerke R^2	Total Predicted Correct / % *	β (S.E)	z^2	$P(z^2)$	Odds Ratio (95% C.I.)
Univariate model							
Δ-ICD / mm	14.636	0.397	76.2	1.148 (0.398)	8.315	0.004	3.151 (1.444-6.873)
Volume / mm^3	9.648	0.277	69.0	0.026 (0.010)	6.790	0.009	1.026 (1.006-1.046)
Interactio	5.700	0.452	78.6	0.014	5.894	0.015	1.014 (1.003-

n term **				(0.006)			1.026)
Bivariate model							
Δ-ICD / mm	19.474	0.501	73.8	1.080 (0.446)	5.867	0.015	2.944 (1.229-7.053)
Volume / mm^3				0.024 (0.012)	3.728	0.054	1.024 (1.000-1.049)

* cohort default 59.5 %.** (Δ-ICD / mm) x (Volume / mm^3)

The ratio of non-invasive to invasive-type Knosp grade was 52:48 for those who had no further intervention, and 35:65 for those who had. Knosp grade was not significantly associated with further intervention (χ^2 = 5.6, P = 0.233). Further intervention had not been carried out in any case of GTR, STR or residuum less than 1 mm (N=14). Analyzing only patients with post-operative residuum greater than 10 mm (N=28), Δ-ICD remained a predictor of secondary intervention (expB: 3.771, 95% C.I: 1.270-11.194, P = 0.017).

Discussion

We have re-iterated that ICD is a simple MRI measurement that is reliable within and between observers, despite the small distances involved[4]. Our study re-affirms that after transsphenoidal debulking of non-functioning pituitary adenoma the sella contracts medially; though the magnitude of this contraction varies substantially. It also demonstrates that abnormal cavernous-carotid anatomy does, to some degree, normalize following surgery.

The critical result of this study was the finding that Δ-ICD was a superior predictor of recurrence, and was largely independent of pre-operative tumor volume. This relationship is unlikely to be causal; more likely a tumor's mechanical ability to laterally expand the sella is rooted in unfavorable biology. We found that pre-operative tumor volume was a significant predictor of progression to a second surgery (recurrence), as suggested by the literature.[14,16] The B-value was close to zero however, so this finding is tenuous. Although the bivariate model had a better quality of fit than univariate models (see Table ~~1~~2: χ^2, $R^2_{nagelkerke}$), the contribution of tumor volume to recurrence prediction lost significance, whereas Δ-ICD maintained significance. Overall, this suggests that Δ-ICD could serve as a lone prognostic marker, or perhaps supplementary to pre-operative tumor volume.

Both a greater mean Δ-ICD and a greater mean pre-operative tumor volume were observed for those who needed early- to medium-term re-intervention. However, correlation between Δ-ICD and tumor volume was weak (R = 0.35), and individual patient analysis revealed numerous cases of relatively small tumors that showed high Δ-ICD (see Fig.2). This is consistent with prior reports investigating ICD contraction, finding that it was not well predicted by tumor size/volume.[11,12] Despite this, Δ-ICD is evidently contingent upon the prior existence of tumor sufficient to expand the sella before it can 'relax' and contract. However, Δ-ICD and volume are different physical measurements, not merely surrogates for each other. Importantly, Δ-ICD appears to better reflect the combination of the mechanical properties of the tumor and the reaction of its environs. For example, soft and hard tumors may have equal volume, but will have different mechanical properties. Mechanical properties of the tumor may hinge on important biological features, for example cellular density, fibrosity, vascularity. Perhaps these are the causal features underlying recurrence, and which Δ-ICD illuminates.

ICD contraction supports a hypothesis that lateral sella expansion is an elastic process. This suggests that the sella is under raised pressure pre-operatively, and that Δ-ICD is a measure of sella 'relaxation' after intra-sella pressure normalizes following surgery. As such Δ-ICD may be a retrospective surrogate for intra-sella pressure. The determinants of pituitary tumor growth patterns remain poorly understood: some tumors preferentially grow upwards and balloon over the sella towards the optic apparatus whilst others preferentially invade into the sphenoid sinus or cavernous sinuses. Anatomical factors such as the extent and pattern of pneumatization of the sphenoid are probably important, as are variation in size and continuity of the lateral boney margins of the sella,[18] diaphragma sellae foramen size and chiasmal topography.[19,20] However, even with all this potential variation, we have shown that changes in the easily-measured ICD may have a prognostic use.

The 95% confidence interval for Δ-ICD was large (see Table ~~1~~2), indicating the logistic model would benefit substantially from a larger cohort to generate better certainty of the B-value. Both the blinding of observers to outcome and measurement consistency between observers contribute to the reliability of our findings. However, validation of our findings requires testing our regression model on an additional cohort, ideally prospectively collected. Our study supports an uncoupling between Δ-ICD and tumor volume, which we did not expect. It is unclear if a more precise calculation of tumor volume (e.g. slice-by-slice perimetry) would have changed the findings, but appears unlikely.[17] Conceivably, more invasive tumors with more eccentric morphology, could have had their volume underestimated in this study.[17] However, in real-world practice, detailed volumetric tumor measurement is rarely carried out.

The simplicity and ease of Δ-ICD measurement makes for an attractive radiographic tool for rapid and early post-operative prognostication. There is a paucity of evidence-based guidelines for follow-up MRI scanning after surgery for non-functioning pituitary adenomas. Current guidelines mostly reflect practical considerations and patient preference but are somewhat arbitrary.

Conclusions

For most patients, ICD falls following surgical excision of a non-functioning pituitary macroadenoma. The magnitude of the reduction is uncoupled from pre-operative tumor volume. A greater Δ-ICD was associated with recurrence requiring reintervention.

Although requiring further investigation, early post-operative Δ-ICD shows promise as a prognostic marker in identifying which tumors will have clinically relevant recurrence.

Conflict of interest

None

References

1. Velayudhan V, Luttrull MD, Naidich TP. Chapter 14. Sella Turcica and Pituitary Gland. In: *Imaging of the Brain*. 1st ed. Expert Radiology Series. Philadelphia: Saunders/Elsevier; 2012:22.

2. Banu MA, Guerrero-Maldonado A, McCrea HJ, et al. Impact of skull base development on endonasal endoscopic surgical corridors. *Journal of Neurosurgery: Pediatrics*. 2014;13(2):155-169. doi:10.3171/2013.10.PEDS13303

3. Tatreau JR, Patel MR, Shah RN, et al. Anatomical considerations for endoscopic endonasal skull base surgery in pediatric patients. *The Laryngoscope*. 2010;120(9):1730-1737. doi:10.1002/lary.20964

4. Nunes CF, Cabral GAPS, Mello Junior JO, Lapenta MA, Landeiro JA. Pituitary macroadenoma: analysis of intercarotid artery distance compared to controls. *Arquivos de Neuro-Psiquiatria*. 2016;74(5):396-404. doi:10.1590/0004-282X20160046

5. Ahmadipour Y, Lemonas E, Maslehaty H, et al. Critical analysis of anatomical landmarks within the sphenoid sinus for transsphenoidal surgery. *European*

Archives of Oto-Rhino-Laryngology. 2016;273(11):3929-3936. doi:10.1007/s00405-016-4052-z

6. Serra C, Staartjes VE, Maldaner N, et al. Predicting extent of resection in transsphenoidal surgery for pituitary adenoma. *Acta Neurochirurgica*. 2018;160(11):2255-2262. doi:10.1007/s00701-018-3690-x

7. Lin B-J, Chung T-T, Lin M-C, et al. Quantitative analysis of anatomical relationship between cavernous segment internal carotid artery and pituitary macroadenoma: *Medicine*. 2016;95(41):e5027. doi:10.1097/MD.0000000000005027

8. Manara R, Gabrieli J, Citton V, et al. Intracranial internal carotid artery changes in acromegaly: a quantitative magnetic resonance angiography study. *Pituitary*. 2014;17(5):414-422. doi:10.1007/s11102-013-0516-y

9. Yilmazlar S, Kocaeli H, Eyigor O, Hakyemez B, Korfali E. Clinical importance of the basal cavernous sinuses and cavernous carotid arteries relative to the pituitary gland and macroadenomas: quantitative analysis of the complete

anatomy. *Surgical Neurology*. 2008;70(2):165-174. doi:10.1016/j.surneu.2007.06.094

10. Mascarella M, Forghani R, Di Maio S, et al. Indicators of a Reduced Intercarotid Artery Distance in Patients Undergoing Endoscopic Transsphenoidal Surgery. *Journal of Neurological Surgery Part B: Skull Base*. 2015;76(3):195-201. doi:10.1055/s-0034-1396601

11. Sasagawa Y, Tachibana O, Doai M, Akai T, Tonami H, Iizuka H. Internal carotid arterial shift after transsphenoidal surgery in pituitary adenomas with cavernous sinus invasion. *Pituitary*. 2013;16(4):465-470. doi:10.1007/s11102-013-0492-2

12. Serra C, Maldaner N, Muscas G, et al. The changing sella: internal carotid artery shift during transsphenoidal pituitary surgery. *Pituitary*. 2017;20(6):654-660. doi:10.1007/s11102-017-0830-x

13. Knosp E, Steiner E, Kitz K, Matula C. Pituitary Adenomas with Invasion of the Cavernous Sinus Space: A Magnetic Resonance Imaging Classification Compared with Surgical Findings. *Neurosurgery*. 1993;33(4):610-618. doi:10.1097/00006123-199310000-00008

14. Chang EF, Zada G, Kim S, et al. Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. *Journal of Neurosurgery*. 2008;108(4):736-745. doi:10.3171/JNS/2008/108/4/0736

15. Losa M, Mortini P, Barzaghi R, et al. Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. *Journal of Neurosurgery*. 2008;108(3):525-532. doi:10.3171/JNS/2008/108/3/0525

16. Ho R-W, Huang H-M, Ho J-T. The Influence of Pituitary Adenoma Size on Vision and Visual Outcomes after Trans-Sphenoidal Adenectomy: A Report of 78 Cases. *Journal of Korean Neurosurgical Society*. 2015;57(1):23. doi:10.3340/jkns.2015.57.1.23

17. Davies BM, Carr E, Soh C, Gnanalingham KK. Assessing size of pituitary adenomas: a comparison of qualitative and quantitative methods on MR. *Acta Neurochirurgica*. 2016;158(4):677-683. doi:10.1007/s00701-015-2699-7

18. Wang J, Wang R, Lu Y, Yao Y, Qi S. Anatomical Analysis on the Lateral Bone Window of the Sella Turcica: A Study on 530 Adult Dry Skull Base Specimens.

International Journal of Medical Sciences. 2014;11(2):134-141. doi:10.7150/ijms.7137

19. Campero A, Martins C, Yasuda A, Rhoton AL. Microsurgical anatomy of the diaphragma sellae and its role in directing the pattern of growth of pituitary adenomas. *Neurosurgery*. 2008;62(3):717-723. doi:10.1227/01.neu.0000317321.79106.37

20. Won H-S, Han S-H, Oh C-S, Lee J-I, Chung I-H, Kim SH. Topographic variations of the optic chiasm and the foramen diaphragma sellae. *Surgical and Radiologic Anatomy*. 2010;32(7):653-657. doi:10.1007/s00276-010-0661-1

NUFFIELD DEPARTMENT OF SURGICAL SCIENCES

Oxford Functional Neurosurgery

Mr Ashley Raghu BSc (Hons), MBChB-DPhil student, Oxford Functional Neurosurgery, Level 6, West Wing, John Radcliffe Hospital, Oxford. OX3 9DU

Dear Professor Link,

Thank you kindly for your response and the peer-review from your journal. See below our responses to your reviewers with reference to the relevant revisions of the manuscript.

Reviewer: 1

1. ...There is no description of clinical characteristics in 42 patients apart from age and gender. More clinical information must be mentioned and assessed. These include primary or second surgery, cystic or solid tumor, invasive tumor or not, sellar floor destruction or not, et al.

- All 42 patients in our study underwent primary surgery; change in ICD was looked at solely for those surgeries.
- We have now included the number of tumors which had a major cystic component.
- We have now included the Knosp grade.

2. In general, predictive factors of recurrence in nonfunctioning adenomas include presence of residual tumor, the Ki67 (MIB-1) index, histological subtype, age, etc. Was there any correlation between the change in ICD and tumor proliferation marker (MIB-1)?

- Unfortunately, only 2 of our 42 patients had MIB-1 reported. Historically, this has not been a popular test for pituitary adenoma among neuropathologists at our institution. It is now starting to be used more.
- Histological subtype was reported.

3. The number of patient who required additional treatment was quite high, more than 40% (17/42). How many of them achieved total tumor resection? If the tumor is only partially resected, it may be meaningless to assess ICD.

- We have now included data on post-operative residuum.
- We do not understand why our findings would lack relevance or interest in the case where tumor is only partially resected. Our finding that this simple measure appears to have good predictive value remains the same. Partial resection is also a common occurrence with these tumors. For example, if tumor is in the cavernous sinus, gross-total resection is rarely achieved, and pursuing it may well be injudicious.

Reviewer: 2

...It is a novel observation to link ICD reduction to recurrence rates, which will require further larger studies to be meaningful.

- We agree that this will require replication in a larger cohort to be meaningful. We hope publication of this data will lead others to explore this.

I think the authors need to add data on extent of resection, to make a causal link with ICD. Therefore, initial Knosp grade should be included, more information on tumour type (functioning vs NFA) and Ki 67.

- At this stage establishing a causal link is beyond the ambition and scope of this work. Nonetheless, we think this study presents an interesting correlative observation.
- As above: Knosp grade has now been included in the manuscript.
- All tumors in the study were clinically non-functioning macroadenoma.
- As above: we are regrettably unable to provide data on Ki-67 as this was not carried out in 40 of our 42 patients.

Importantly, the extent of resection/residual tumour must be included as this is an important factor in recurrence.

- As above: we have now included data on post-operative residuum.

Could the ICD have a bearing on the ability to achieve a complete resection leading to the findings seen in this study.

- This is a very interesting question. We suspect it might be a factor, but that there will generally be more important determinants, e.g. cavernous sinus involvement, supra-sellar component etc. There was no correlation between pre-operative ICD and extent of resection in our cohort.

The extent of resection is clearly relevant for tumor recurrence. We have now included an assessment of this that we hope will satisfy the reviewers. Likewise, we have now assessed Knosp grade. These constitute our major revisions to our manuscript. We agree that this adds to the completeness of the study.

In predicting recurrence, there are many known factors which could be used in a statistical predictive model for clinical practice. As the reviewers suggest, Ki-67, histological type, age and post-operative residuum are some of these. It was not the purpose of our research to generate a multifactorial model for clinical prediction. We were attempting to identify whether change in ICD predicted recurrence, and to probe its independence by exploring whether this was explained by tumor volume (i.e. was a surrogate). We chose this strategy by favouring a hypothesis-driven over a data-driven approach.

In our manuscript we looked at pre-operative tumor volume; it was pointed out that variation in this seemed to be the most rationale mechanism for variation in post-operative decrease in ICD. Conversely, we cannot see an obvious mechanism by which the extent of resection would be causally related to post-operative decrease in ICD, so that less residuum would correspond to a smaller decrease in ICD. As large residuum conveys higher risk of recurrence, this is the relationship that would be required for residuum to explain the higher risk of recurrence with greater decrease in ICD. However, if anything, the relationship would be expected to be opposite (more residuum – less decrease in ICD). Similarly, such a mechanism is unclear but perhaps more plausible for Knosp grade. As such, this was why we did not originally include these variables in our submission. Now examined, neither variable was significantly associated with decrease in ICD in our cohort. Presence of residuum was important for recurrence, and Knosp grade less so.

We hope that we will have answered the reviewer's comments to their satisfaction. In addition, we hope that we have further clarified our rationale and strategy regarding this study.

Thank you for considering our article for publication in your journal.

Kind regards,

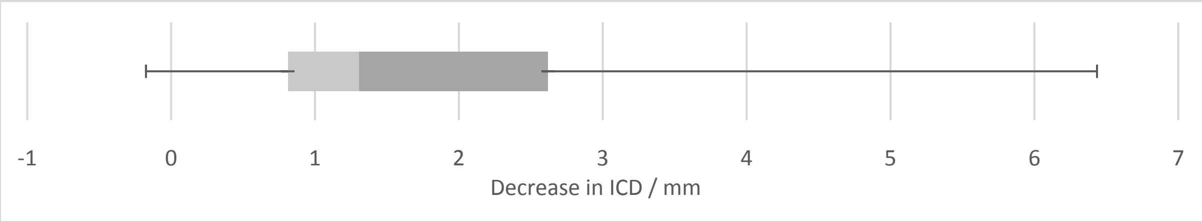
Ashley Raghu, corresponding author

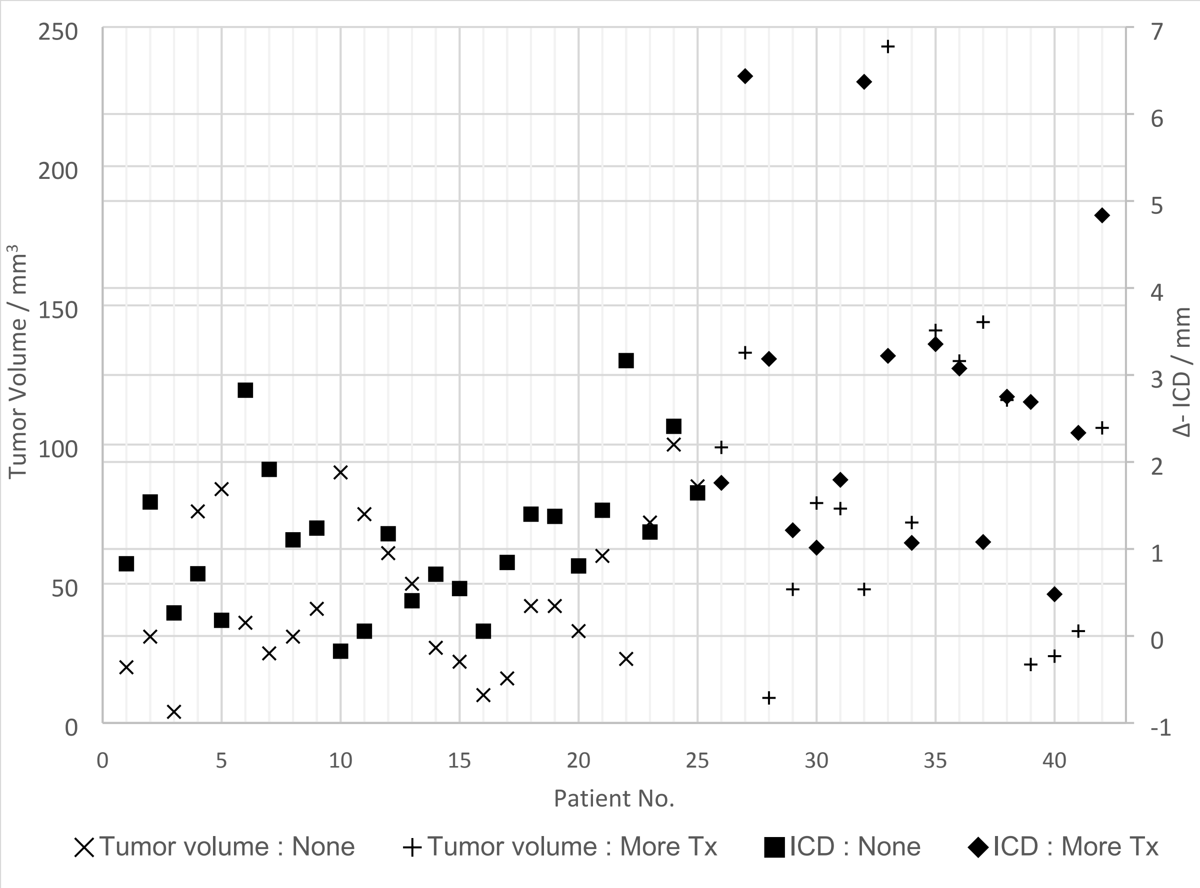
Hannah Flower,

Patrick Statham,

Paul Brennan,

Mark Hughes


-1
0
1
2
3
4
5
6
7
Decrease in ICD / mm



Tumor Volume / mm³
Δ- ICD / mm
Patient No.
Tumor volume : None
Tumor volume : More Tx
ICD : None
ICD : More Tx